Pharmaceutical Residues in the Environment - New European Integrated Programs Required

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A variety of pharmaceuticals has been detected in many environmental samples worldwide. Given the unpredictable and possible severe effects, there is substantial public concern about the environment contamination with pharmaceutical residues. Nevertheless, only preliminary measures aimed at protecting the environment from adverse effects of pharmaceutical pollutants are in place; these measures must be supplemented by integrated programs. This paper provides an overview of recent scientific research on the sources and occurrence of pharmaceuticals in the environment, an up to date review of the EU regulations and directives on the environmental protection with respect to pharmaceuticals and emphases the problems encountered in the implementation of the protection measures.

Keywords: pharmaceutical residues, monitoring programs, environment protection

In the recent years, environment contamination with pharmaceutical residues has become a frequently recurring phenomenon benefiting also of media attention [7]. In contrast to most other chemical pollutants, pharmaceuticals are biologically active molecules, designed to trigger a biological processes in humans or animals bodies, usually active at very low concentrations [38]. As the pharmaceuticals target molecules are present in other species as well, those compounds have the potential to affect other organisms from the environment. Pharmaceuticals have been recognized as a potentially hazardous group of substances with respect to the environment [4, 7].

Although the occurrence of such substances in the environment have been intensively studied [31, 45, 46, 52] there is a lack of knowledge for long-term effects on human and especially on ecosystems of the exposure to low concentrations of such compounds and their mixtures [4]. Recent studies demonstrated that measured environmental concentrations of antibiotics are high enough to exert a selective pressure on clinically relevant bacteria that may lead to an increase in the prevalence of resistance [13, 38].

Soil contamination with pharmaceutical compounds can lead to qualitative and quantitative effects on resident microbial soil populations [3], disturbances in soil functioning [49], or to plants growth inhibition [37].

At the present, statements about the behaviour of pharmaceuticals in the environment are highly speculative. However, OECD (The Organization for Economic Co-operation and Development) tests show that 95% of the pharmaceuticals studied are not readily biodegradable [23].

Therefore, given the unpredictable and possible severe effects, there is substantial public concern about the environment contamination with pharmaceuticals.

This paper provides an overview of recent scientific research on the sources and occurrence of pharmaceuticals in the environment, an up to date review of the EU regulations and directives on the environmental protection with respect to pharmaceuticals and emphases the problems encountered in the implementation of the environmental protection measures.

Sources of pollution

The primary sources of human pharmaceutical contamination are represented by domestic, urban, hospital, and industrial wastewater [2, 7, 57]. Close attention must be paid to hospital wastewater, which could contain various potentially hazardous substances: chemical substances used for cleaning and disinfection, antibiotics, sedatives and anesthetics, cytotoxic drugs, immuno-suppressants [7].

Veterinary pharmaceuticals used in agricultural livestock become also a source of environment contamination. The disposal of sewage from intensive livestock farming sites, effluents from intensive aquaculture systems, and manure application have been also recognized as a source of veterinary drug contamination of soils and water [33]. Soil contamination with pharmaceuticals results from the use of contaminated manure as fertilizer on agricultural land.

The main classes of veterinary compounds which can reach the soil, surface and groundwater sites are antibacterials cephalosporins, macrolides, fluoro-quinolones, sulfonamides; antiparasitic agents; antifungals; growth promoters and hormones; coccidiostats drugs.

Analytical methods for the detection of pharmaceuticals in the environmental matrices

Today, the new analytical techniques allowed the development of highly sensitive detection methods that can detect and quantitate organic chemicals, including pharmaceuticals, at concentrations ranging from 1-100 ng/L in different environmental matrices.

Liquid chromatography combined with tandem mass spectrometric detection – either triple-quadrupole, ion-trap multi-stage or orbitrap MS – is the preferred technique in a large majority of residue classes [6, 29, 45, 46, 51]. As sample treatment, solid-phase extraction (SPE) or liquid-liquid microextraction are the most popular [6, 9, 50].

Regarding the validation and the performances criteria of the analytical methods for pharmaceutical compounds detection in the environmental matrices, at the time, there is no standard methods, no maximum permitted limit and no minimum required performance level adopted.

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The Decision 657/2002/EC defines the performance criteria for analytical methods for the detection of veterinary drug residues in live animals and animal products. Specific requirements of those regulations enforce the application of high analytical techniques for the confirmatory purpose. Anyway the Decision 657/2002/EC and related documents refer to the detection of veterinary drug residues in animal products not in the environmental matrices.

Lack of the regulation in the environmental area leaded to adapting the existing regulation to environmental analysis [46]. The Decision 2002/657/EC was applied also for the detection of pesticides in water samples concerning the number of the identification points [36].

Occurrence of the pharmaceutical residues in the European environment

The existence of drugs in environmental waters was first reported in the 1970s by Tabak and Brunch. Nowadays, a vast amount of data is available on this subject in the scientific literature, but unfortunately they usually refer to small-scale investigations on a restricted number of drugs.

The most frequently analysed and detected classes of pharmaceuticals are anti-inflammatory drugs, analgesics, antibiotics, lipid regulators, steroids and related hormones, beta-blockers [6, 29, 31, 51]. Carbamazepine, diclofenac, ibuprofen, propranolol, erythromycin, ciprofloxacin, sulfamethoxazole are some of the most popular compounds for which studies report widespread occurrence in the aquatic environment.

Table 1
PHARMACEUTICALS DETECTED IN THE ENVIRONMENT

Pharmaceuticals	Sampling site	Matrix	Reference
Diclofenac, carbamazepine, clofibric acid, sulfamethoxazole, ibuprofen, trimethoprim, oxazepam, codeine	Germany	Sewage, Surface, and Drinking Water	Wilken et al., 2000;[56]
Sulfadimidin, clindamicin, erytromicin, trimetoprim, sulfametoxazole, ofloxain	Germany, North Rhine-Westphalia	Soil/surface water	Christian et al., 2003;[12]
Cloramphenicol, sulfamethoxazole, ketoprofen, naproxen, carbamazepine	Germany, Rhine river basin	River water	Laak et al., 2010;[48]
Oxytetracycline, sulfachlorpyridazine	The UK, River Trent at Shardlow, Derbyshire/River Soar catchment area in north west Leicestershire/Osgathorpe, Leicestershire	River water, surface water, ground water	Blackwell et al., 2004;[6]
Acetylaminophenazone, pentaoxifilline, ibuprofen, formylaminophenazone, p-chlorophenyl sulfone, oxetanamine, triclosan, carbamazepine, codeine, diazepam, cyclophosphamide	Romania, Somes River	Surface water	Moldovan, 2006;[40]
Carbamazepine, diclofenac, sulfamethoxazole, trimethoprim, thiabendazole, clotrimazole, trimethoprim, erytromicine ciprofloxacine.	Romania, eastern Romania: Danube river, Prut river, Siret river, Jijia river; south Romania: Prahova river – puncul de recotare	River water	Chitescu et al., 2014;[10]
Carbamazepine, diclofenac, sulfamethoxazole, indomethacin, naproxen, tylosin, thiamulin	Danube river on Romanian terithory	River water	Chitescu et al., 2015;[11]
Chlortetracycline, enrofloxacin, ciprofloxacin, sulfadimideine, trimetoprime,	Austria, agricultural fields	Soil	Martı´nez-Carballo, et al., 2007;[39]
Carbamazepine, diazepam, fenofibric acid, propranolol, trimethoprim sulfamethoxazole	Portugal, Duoro River	Surface water	Madureira et al., 2010;[41]
Carbamazepine, ibuprofen, diclofenac, naproxene, 17α-ethylestradiol	Czech Republic	Drinking water	Kozisec et al., 2013;[35]
Diclofenac, ibuprofen, propyphenazone, clofibric acid	Greece, urban areas	Sewage water	Koutsouba et al., 2003;[34]
Sulfamethoxazole	Israel, deep phreatic aquifer in Glil Yam, 15 km north of Tel Aviv	Groundwater	Avisar et al., 2009;[5]
Sulfamethoxazole, carabamazepine, diclofenac, erythromycin, ketoconazole, fluconazole, thiabendazole, carbendazim, propiconazole	The Netherlands: Zaar River, Huizen lake, Amsterdam channels, channels from agricultural area	River water, surface water	Chitescu et al., 2012;[9]
Salicylic acid, bezafibrate, ibuprofen, diclofenac, carbamazepine, chloramphenicol, paracetamol, clofibric acid, metoprolol, sulfamethoxazole,	The Netherlands	Drinking water	Stolker et al, 2004;[46]

fenofibrate, Dehydroerythromycine			
Diclofenac, ibuprofen, naproxen, ketoprofen	Hungary, Danube river	River water	Helenkár et al., 2010;[30]
Diclofenac, ibuprofen, naproxen, ketoprofen	Poland, Warta river	River water	Kasprzyk-Horden et al., 2008;[32]
Citalopram, mianserin, sertraline, moclobemid, venlafaxine	Poland, Vistula and Utrata rivers/ Warsaw	River water, Drinking water	Giebułtowicz et al., 2014;[26]
Carbamazepine, trimethoprim, erythromycin, diazepam, sulfamethoxazole	Serbia, Danube river basin	River water/Sediments	Radovic et al., 2012;[44]
Ibuprofen, carbamazepine and metabolites, acetaminophen	Serbia	Waste, surface, tap, groundwater	Petrovic et al., 2014;[43]
Erythromycin-H2O, clarithromycin, and azithromycin	Spain, rivers: Noguera Ribagorc¸ana, Ter and Llobregat, located in Catalonia	River water	Abuin et al., 2006;[1]
Carbamazepine, diazepam, ofloxacin, fenofibrate, ciprofloxacin, codeine, metoprolol, propanolol, acetaminophen and clofibric acid	Spain, areas of the Valencian Community, Albufera Natural Park, Prat Torreblanca-Cabanes and the marshes of Oliva-Pego, Silla and Moros.	Soil/sediments	Vazquez-Roig et al., 2010;[51]
Chlortetracycline,doxycycline, oxytetracycline, tetracycline	Spain, surrounding area of Valencia city	Soil	Andreu et al., 2009;[63]
Decoquinate, sulfamethazine, sulfamethoxypyridazine and trimethoprim	Spain, rural areas in Galicia	River water	Igresias et al., 2014;[31]
Sulfonamides	Spain, Ebro river basin	River water	García-Galán et al., 2011;[25]
Ofloxacin, ciprofloxacin, codeine, trimetoprime, diazepam, propanolol, metoprolol, sulfamethoxazole, diclofenac, acetaminofen, carbamazepin, ibuprofen, clofibric acid.	Spain, Mediterranean wetland L'Albufera, Valencia	Water/Soil/Sediments	Vazquez-Roig et al., 2011;[52]
17 pharmaceuticals including atenolol, caffeine, ibuprofen, roxithromycin and sotalol	Belgium, Maas and the Albert channel	River water	Vergeynst et al., 2014;[53]
Propanolol, nimesulide, furosemide, carbamazepine, ranitidine, metronidazole, paracetamol, and atorvastatin	Italy, Po river and all its effluents	River water	Ferrari et al., 2011;[24]
Fluoroquinolone and sulphonamides antibiotics	Swiss	Waste / surface water	Adler et al., 2000;[2]
Cyprofloxacine, norfloxacine	Swiss	Wastewater	Golet et al., 2002;[27]

Table 1 presents an indicative list of pharmaceuticals detected in the environment in different European countries. No information was available for Cyprus, Croatia, Bulgaria, Slovenia, Ukraine and other eastern European countries.

The results of a literature review on German monitoring data of pharmaceuticals in the environment have recently been published[8]. The study showed that 156 pharmaceuticals have been detected in Germany in the following matrices: surface water, groundwater, drinking water, sewage effluent, sewage sludge, manure, soil, and sediment. For 20 substances, the highest concentrations measured were between 0.1 and 1 mg/L in groundwater; for 13 other substances, the highest values were more than 1mg/L. A maximum value reported for carbamazepine (anticonvulsant) was more than 3 mg/L [56].

The relevant findings of the monitoring program in the basin of the Po river (2006-2007) refer to carbamazepine concentrations between 2-115 ng L^{-1} and paracetamol concentrations between 34-3590 ng L^{-1} [24].

Analysis of samples collected from Danube river basin in Romania, revealed concentrations of carbamazepine of 20-49 ng L^{-1} and diclofenac lower than 20 ng L^{-1} in the Danube and a maximum of 166 ng l^{-1} in the Arges river [11].

On the basis of concentrations found in water bodies during monitoring (maximum measured environmental concentration MEC_{max} > predicted no-effect concentration PNEC) scientists assume that substances such as carbamazepine and diclofenac have a potential ecotoxicological impact and must be treated as high-priority hazards.

Legislative aspects

Authorization of pharmaceuticals is subject to EU legislation in order to supplement or specify regulations to environment protection.

Within Europe, the requirement for an environmental safety, part for the registration of pharmaceuticals, was first described in Directives 93/ 39-40/EC. To the date, the marketing of veterinary medicinal products is regulated in EU by Directive 2001/82/EC relating to veterinary medicinal products, and Directive 2001/83/EC relating to medicinal products for human use, supplement and specifying regulations pertinent to environment protection. However, these regulations have hardly been applied to date in all EU states member.

During the last years, the environmental risk assessment of human and veterinary pharmaceuticals has been addressed by several regulatory guidance documents: VICH (International Cooperation on Harmonisation of technical requirements for Registration of Medicinal Veterinary products) – Guideline on environmental impact assessment for veterinary medicinal products phase I (2000), and phase II (2005); EMEA/ CHMP/SWP/4447/00/ 2006 - Guideline on the environmental risk assessment of medicinal products for human use; [21] EMEA/CVMP 2008 – Reflection paper on the implementation of directive 2001/ 82/EC, as amended, in respect to the assessment of environmental risk of veterinary medicinal products [22].

According to those regulations, environmental hazards are to be indicated together with the submission of an application for authorisation. The guidelines propose exposure models to estimate the predicted environmental concentration (PEC) of veterinary pharmaceuticals in soil and water. The decision-making scheme (decision tree) has been fixed on a general level – trigger value - and it is indicated that both fate and effects of drugs should be assessed.

One serious deficit in this regulation is the fact the environmental risks are not part of the cost-benefit analysis (Article 26, Directive 2001/83/EC) [17]. The consequence is that authorisation of a human pharmaceutical product cannot be denied for reasons related to environmental protection [8].

Furthermore, there are some inconsistencies between the legislation concerning environmental risk assessment. Guideline for veterinary medicinal products is based on the soil contamination and considers as a trigger value for phase II, the PEC of 100 mg kg^{-1}. The same guide considers the maximum concentration of 1μg L^{-1} in the effluent for drugs used in aquaculture. Where intensive livestock farming are practiced is recommended to calculate the PEC for groundwater and compare with the value of 100 ng L^{-1} as a trigger value of the second stage. On the other hand, the guidance EMEA/CHMP/SWP/4447/00 (2006) [21] considers as trigger value of phase-II the concentration of 10 ng L^{-1} for surface waters.

Therefore, efforts should be done for harmonization of the regulations on environment risk assessment for pharmaceuticals.

Present and future actions

The European Water Frame-work Directive aims to reduce groundwater pollution. Thus far, however, environmental quality EU norms, which must be established according to Annex I of the Directive 2000/60/EC [16], have only been set for nitrate, biocides, and pesticides, but not for pharmaceuticals. A revision of Annexes I and II of the Groundwater Directive by the EU Commission with a provision on pharmaceuticals was adopted in 2013 [20].

For the first time, three pharmaceuticals substances (diclofenac, 17 alpha ethinylestradiol, and 17 beta-estradiol) was explicitly earmarked for study within the framework of EU-wide water monitoring in the recently adopted Directive 2013/39/EC amending Directive 2000/ 60/EC as regards priority substances in the field of water policy [20]. Those compounds were not introduced on the priority substances list, but nominated in the first watch list (which became available in September 2014), in order to gain information on pollutants that might be appropriate for prioritisation but for which there is a lack of information on their occurrence across Europe. Monitoring should be carried out not less than once a year. A requirement of the EU Commission is also to develop a strategic approach to the pollution of water by pharmaceutical substances. However, implementation of these demands is to date inadequate. Though, especially in the Central and North Europe there are actions in order to monitor and reduce the amount of the pharmaceutical pollutants.

During 2007-2012, Germany, The Netherlands, Luxembourg, Switzerland, United Kingdom and France - have worked together in the PILLS project for testing new wastewater treatment technologies for the removal of the pharmaceutical residues Pills final Conference report, 2012).

A database of Pharmaceuticals and Personal Care Products (PPCPs) found in wastewater treatment plants have been developed in 2009 based on information from 117 studies into wastewater from Europe, Brazil and North America [42].

Within AQUA TERRA (project no. 505428) data sets were produced on the occurrence of pharmaceutical compounds in the samples from the Danube river basin (sampled downstream of Vienna, Novi Sad, Budapest, Belgrade) during the sampling campaign in August 2004 [28].

Join Danube Survey reported the monitoring results of a set of 49 emerging contaminants in water samples collected in August – September 2013 from 68 sites along the Danube river and the main tributaries (Joint Danube Survey 3, Final report, 2015).

A comprehensive monitoring study was conducted 2002-2008 in Germany in the Rhine river basin. A list of 126 pharmaceuticals was considered (Laak et al., 2010). Water bodies were tested to determine pharmaceutical pollutants and environmental quality norms were developed as long as no other legislative decisions have been taken.

Switzerland has recently (2011) begun implementing systematic monitoring of groundwater habitats (UBA 30 August 2011: Wasser, Trinkwasser und Gewasserschutz. Lebensraum Grundwasser. Text und Vorträge).

The northern European countries have reached a new stage dealing with this issue. Ten ozone pilot installations for removal of pharmaceutical and Personal Care Products residue from water will be run in Sweden during 2014 (Press release, December 2014).

In order to minimize pharmaceutical pollution in water in Europe, measures regarding disposal medicine were implemented (Directive 83/2001/EU art. 127b) [19]. However, Health Care Without Harm (HCWH) European association released in February 2014 (Brussels) a snapshot report that presents the results of a an European survey suggesting that systems for the collection and disposal of unused medicines across Europe are not effective as too many pharmaceuticals end up in the environment. Furthermore, the report mentions that Cyprus, Greece, Latvia, Luxembourg, Malta, Romania, Bulgaria and Slovenia do not yet have systems in place.

Future actions should consider all European countries and refer to: monitoring strategies should be improved by replacing spot sampling with integrated methods and programs; definition of respective environmental quality standards; inclusion of emerging pharmaceuticals in the revision of EU List of Priority Substances under the Water Framework Directive 2000/60/EC [16]; developing, validation and transfer of analytical multimethod for pharmaceuticals screening in environmental matrix, especially regarding the Eastern Europe, where such methods are not currently applied; routine monitoring of those compounds become subject to regulation.

Conclusions

Considering the available data, we conclude that compounds as pharmaceutical residues are ubiquitous.

During the last decade, efforts have been done for the evaluation and reducing of pharmaceutical contamination of the environment.

Nevertheless, only preliminary measures aimed at protecting the environment from adverse effects of pharmaceutical pollutants are in place; these measures must be supplemented by integrated programs.

The goals of such projects should facilitate identification, prioritization and evaluation of human health and environmental risk; close the gap in knowledge on the environmental behaviour of pharmaceuticals**;** improve the scientific basis of regulatory decision; harmonisation of the water protection legislation.

There is also a need of more screening actions regarding the prevention of uncontrolled discharge of pharmaceuticals in the environment in the Eastern Europe.

Finally, socio-economic measures that may be able to hinder the introduction of such compounds into the environment should be considered.

Acknowledgments: The authors are grateful for the financial support grante POSCCE ID 1815, cod SMIS 48745.

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Manuscript received: 18.12.2015